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THE RELATION OF MODERN CHEMISTRY TO MODERN MEDICINE.*

THE history of the relation of chemistry to medicine is interesting to the physician as well as to the chemist, but has been studied mainly from the standpoint of the latter. From the remotest periods chemistry, or, more accurately, the crude science or art which preceded it, found application in two directions, first, in the treatment of metals or ores or similar bodies to produce something of greater value, and secondly, in the curing of disease or prolonging of life. In both fields of effort the attempts were and remained through some thousands of years of the simplest character. Even in the work of Galen, who flourished two hundred years after Christ and who has been styled the first of the great physicians, there is little which suggests any attempt toward a systematic knowledge of chemical substances. According to the philosophy of the Egyptians and Greeks then current, all things, including the human body, were made up of a limited number of elements or qualities, usually four. With the proper mixture of these the body remained in normal health, but with the qualities out of proportion disease followed which must be attacked through the corrective agency of medicines. Galen's medicines were mostly simple vegetable infusions or extracts of roots, barks and leaves, and the term galenical we still retain to describe the remedies which are essentially indefinite mixtures secured by processes similar in principle to those introduced by

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the Egyptian. After 1,700 years of progress we still find many disciples of Galen among us, and the remedies which are 'purely vegetable,' or advertised to be, find yet among the ignorant the largest sale.

The beginnings of chemical and medical knowledge came to western Europe through the Arab conquest of Spain and in that country were nurtured through many years. Alchemy and theology, however, developed more rapidly and the learned showed greater interest in the transmutation of metals and the saving of souls than in the perfection of means for curing the ills of the body. The system of Galen remained adequate for the needs of physicians through a period of 800 years following the Moorish conquest. It could not be otherwise with miracle shrines in every village and burning fagots for all that doubted.

In the sixteenth century we recognize the first systematic attempts made to improve on the materia medica brought down from Greece and Egypt. Paracelsus began to teach the value of artificial products in the curing of disease, and, although meeting with great opposition, he with his pupils gradually built up a creed which flourished a century and a half. Paracelsus, familiar with the doctrines of the alchemists, and through extensive travels well acquainted also with the operations in metallurgy in many countries, set about to apply the gradually accumulating knowledge to the production of chemical remedies for human ailments. He promulgated a crude theory of the normal conditions of the body and, like Galen, assumed that variations from that normal could be corrected by chemical agents. Civilized as well as uncivilized man has usually been a believer in materia medica, and the notion that arsenic or mercury or antimony or sulphur could build up what disease had torn down possessed an element of plausibility that rapidly attracted adherents. Medicine became, in effect, a branch of applied chemistry and the chief energies of physicians were bent in the direction of medication rather than toward the development of diagnosis. We can not wonder at the subsequent failure of the system, since it grew into a kind of exaggerated empiricism not far removed from quackery. Indeed, it is difficult to realize at the present time how the iatro chemistry developed and flourished as long as it did. It must be remembered that chemical analysis was then quite unknown, and of chemical compounds only such were in use as could be easily made from a small number of native minerals and the simple inorganic acids and alkalies then available. Of the substances called organic very few had been discovered. A system of chemical therapeutics based on so slim a foundation failed, then, because of the wide divergence between what was confidently promised and what experience showed was practically realizable. But while no good came directly from this approach of chemistry to medicine, the indirect results were more important, since the large number of physicians turned chemists accomplished the discovery of many new substances.

We hear little more of the influence of chemistry on medicine through the one hundred years following the decline of the iatro school. Not, indeed, until the time of Lavoisier and his colleagues, when the explanation of the respiration process in its relation to oxidation and combustion and the investigations by the calorimeter on the origin of animal heat called again attention to the possibilities of chemistry in the development of medicine. About the same time came the discoveries of Galvani and Volta, the importance of which was soon recognized. Those were inspiring times for the real science of chemistry newly born, when each day, almost, added some new fact to the rapidly filling store-house. The learned in all lands stood amazed at

the news brought in the journals or just as often in the letters from Paris, or London or even from little Weimar, where the Wahlverwandtschaften reflected the curiosity and enthusiasm of the epoch. There was for a moment danger that the medical-chemical history of the seventeenth century would repeat itself at the beginning of the nineteenth, when oxygen and the galvanic cell began to be hailed in some quarters as offering the key for all mysteries and the cure for all diseases. But the three hundred years following the rise of Paracelsus had produced a new race of thinkers, and only temporarily could men be brought away from a now well-developed and necessary tendency—the collection and investigation of facts.

It is not my purpose to sketch the fruitful work of the next half century, as I wish to speak particularly of a later period, but it must be recalled that the pioneer labors of Dumas, Liebig and Wöhler in organic chemistry made possible the later developments in physiological and pathological chemistry. In this period of great scientific activity it must be admitted, however, that the practical influence of chemistry on medicine was not very great. Each discipline developed largely in its own way, and while the practitioner recognized in physiology and physiological chemistry sciences of great interest and beauty, he was not very clear as to what uses he could make of them except in a few limited directions. Chemistry had become completely divorced from pharmacy and cared nothing for the preparation of remedies, and the applications of chemical analysis which might prove an aid in diagnosis were as yet few and far between. In the eyes of the medical practitioner and medical student chemistry was very theoretical, to be tolerated rather than to be cultivated. I have elsewhere called attention to the almost futile efforts to build up courses in chemistry in the early medical schools of the United States. The efforts failed here as, practically speaking, they failed elsewhere at the same time because of the lack of immediate relationship of the one science to the other. A medical man might just as well be asked to study botany or zoology as chemistry, as far as any really helpful practical application was concerned, excepting, perhaps, in two or three simple tests.

And so the situation remained until about 1860, when the views of Pasteur on alcoholic fermentation and the isolation by the German physiologists of several active soluble ferments or enzymes of the animal body began to attract wide attention and point the way toward an explanation of many processes taking place in the organism. With the growing recognition of the character and importance of the work of the enzymes I think we have the first real tangible evidence of the dependence of medicine on the new chemistry. The doctrine of the ferments as applied to the chemical changes taking place within the body is one, apparently, of indefinite extension, and at the present day, after forty years of trial, it seems more than ever likely to hold its own and be capable of even wider development. In passing, I must add that it would not be fair to claim that the great advances just suggested were all due to the efforts of chemists. On the contrary, many of them were conceived and largely worked out by men who had been trained primarily in medicine rather than in chemistry.

In speaking of the relations of modern medicine and chemistry it may be recognized that they are essentially of three kinds. We have first the very simple and so-called practical relation in which chemistry becomes an aid to medicine in the way of diagnosis. Here analytical chemistry is alone concerned and the chemist is called

upon to determine by tests the normal or pathological character of some body fluid or excretion about which the physician must have information before he can make a correct diagnosis. This work is, of course, extremely important, but, as ordinarily applied, it calls, perhaps, for the lowest order of chemical knowledge and represents the lowest requirement which can be made in the chemical education of the medical student. In the hands of the medical practitioner chemical analysis degenerates usually into a routine performance in which a few very simple and accurate tests are carried out in a marvelously inaccurate manner. Medicine is as yet very far from availing itself of the great aid which analysis is ready to offer in the solution of its practical problems in every-day experience, and this is largely due to the fact that in most of our medical schools instruction in chemistry stops before the student has become sufficiently familiar with the real science to feel at home in its applications. All medical students learn something about sugar and albumen and they usually are able to apply their laboratory acquisitions in later practise. But the same can not be said of their experience with acetone or indican or the aromatic sulphates, for example. These, too, certainly have a meaning, and the student has probably learned the tests for them in his laboratory work. But, unfortunately, their relations to disease are less tangible; their bearings do not become clear without a greater mental effort, and hence the once acquired facility is allowed to slip away, or to degenerate into a valueless routine, in which an assumed accuracy may be wholly illusory.

Supposing, however, that the medical man's knowledge of analytical chemistry is full enough and satisfactory for the purpose, and that he continues to practise and even improve upon the tests which he has learned, something more is still desirable or necessary. Much that should be possible in diagnosis is often lost because of the difficulty in connecting that which is shown by analysis with what it indicates or depends upon. The value of analytical chemistry in medicine soon reaches a limit unless it is accompanied by a very much fuller knowledge of general physiological chemistry than is usually acquired. And, moreover, while routine analytical work may be extremely important, in many cases really essential to diagnosis, it is far from representing the major service which chemistry may render to medicine. By analytical tests we are able to measure some of the effects of certain reactions taking place within the body, but the causes of the reactions and the relations of the things reacting involve ordinarily much deeper problems than those of simple analysis. An illustration may be given. Some years ago Ehrlich introduced a valuable test in the examination of urine which is commonly known as the diazo test, and which depends on the formation of an azo color when a certain reagent is added to the urine. To complete the reaction some aromatic product must be furnished by the secretion, and the presence of this was supposed at one time to be indicative of a definite pathological condition. Later, through more extended clinical observations, it seemed possible to connect it with still other conditions, and then a long discussion arose as to the limits and usefulness of the reaction. Among the many papers published in the discussion some have been good and some bad, even absurdly bad, because they overlooked wholly the essential conditions of the reaction considered from the chemical standpoint. It is evident that many of the writers on the subject were unfamiliar with the chemistry involved in the diazo combination and were, therefore, led to absurd expressions. To fairly comprehend a problem of this kind

a good knowledge of elementary organic chemistry is necessary, and it is essential also that one should have some idea of the part played by bacteria in the organism in producing complex aromatic substances from the disintegration of proteins, since the indications here are often of great importance.

And this brings us to consider the second type of relation between chemistry and medicine, a relation which involves the question of organic synthesis or disintegration in the animal body. At an earlier stage in the discussion it was assumed that, Topsy like, things 'just growed that way.' Later the mysterious electricity and still more mysterious vital force were called in to account for everything not easily explicable by known chemical or physical means. While it is probably true that many of the phenomena of life are and will remain quite beyond our power of explanation, and that here as elsewhere we must accept the *ignoramus* and *ignorabimus* of Du Bois Reymond as final, we are coming, on the other hand, to the recognition of the comparative simplicity of other problems, the solution of which falls within the province of the new physiological chemistry. Medicine will be the chief gainer by these investigations.

It was certainly an auspicious day for chemistry and medicine also when Pasteur developed his biological theory of alcoholic fermentation. Not long after came the work of Kühne, Brücke and others on the enzymes, already referred to, and finally Buchner to clearly demonstrate the long-suspected enzymic character of the yeast ferment. Practically all recent work in this direction has gone to show that so-called organized fermentations are all dependent in turn on enzymic ferments contained within the cells. This distinction may probably be made: in the yeast fermentations, for example, the sugar to be converted is drawn into the cell, and the products, alcohol and carbon dioxide, formed by the zymase, are in turn excreted. In diastasic and similar fermentations, on the other hand, certain cells produce an active ferment which is discharged to do its work outside the generating cell. The difference is thus seen to depend on the place where the reaction occurs, which is not a very important point. The ferments are essentially complex chemical substances, able to bring about various reactions nearly all of which are of exothermal character. Of the nature of many of these reactions we have pretty accurate knowledge, although of the exact mode of action of the enzyme itself our knowledge is scanty. For the present purpose, however, it is sufficient to recognize that these reactions are chemical and we are in a position to trace their bearing on medical problems.

The simplest problems of enzyme action we have in the work of some of the so-called digestive ferments. In the changes wrought in starch by the saliva and by one of the pancreatic ferments the chemical action is one of hydrolysis and very similar to that occurring commonly in the vegetable world. In the germinating seeds, when starch becomes sugar to feed the developing plantlet, water is added through the aid of diastasic ferments, and later, in the ripening of many fruits the same kind of a reaction takes place. These effects, however, are not peculiar to the enzymes; experiment shows that the same starchy substances acted upon by weak acids pass through the same series of changes occurring in the body, and even prolonged heating with water has the same general effect. The hydrolytic and purely chemical nature of carbohydrate digestion becomes at once apparent. What happens in the digestion of fats is equally simple. Here, too, hydrolysis plays the most important part and the work of the lipase enzymes can be

duplicated in the vegetable kingdom and also in the laboratory by the aid of the simplest of inorganic reagents. A far more difficult problem for a long time was to account in any way for the changes taking place in the digestion of proteins. The presence of a proteolytic enzyme in the gastric juice was recognized definitely by Brücke over forty years ago, and about the same time a substance called trypsin was found in the extract of the pancreas. These substances acting on proteins under certain conditions convert them into a series of intermediate and end products about which an enormous literature has been developed. In the course of the long discussion it was discovered that many of the products which are formed by the enzymes may be obtained by the action of weak acids or alkalies, or water even at an elevated temperature, on the original proteins, and finally it was shown that an increase of weight follows in these cases as in the case of the addition of water to starch. All this evidently places the phenomena of protein digestion in the group of hydrolytic reactions, along with the much simpler starch and fat reactions. The digestion processes are, therefore, chemical, and the only thing about them which remains mysterious is the fact that from one set of body cells a ferment working in acid medium is produced, while from a second set of cells a somewhat similar ferment working in an alkaline liquid is secured. Furthermore, all these changes seem to belong to the great group of catalytic reactions, of which more will be said presently.

The general character of these operations was pretty distinctly fixed years ago and their importance clearly recognized. The chemical nature of the several enzymes themselves, however, is not known; the commercial products called pepsin, diastase, etc., are merely crude mixtures of which the active substances make up but a small part. The investigation of the properties of these enzymes opened the way for the study of other reactions peculiar to the animal organism, which are likewise undoubtedly of enzymic origin. In fact, the view is gradually gaining ground that by far the largest number of the body functions involve in some way the action of enzymes. The digestion phenomena are among the simplest and most readily observed, but patient investigation has brought to light other reactions as truly enzymic as these. In the liver alone there are no less than ten well-defined processes in progress, in the initiation of which enzymes are concerned. For the maintenance of the wellbeing of the body the proper performance of these processes is as essential as is digestion itself. In a general way most of these processes have been known or suspected for years, but they were supposed to depend on some peculiar vital action of the liver cells themselves. The situation here is analogous to that regarding the mode of action of the yeast cell, but most investigators now consider the enzymic or chemical theory as well established. The liver may, indeed, be compared to a laboratory in which important syntheses and decompositions are constantly taking place. Some of these are of such a character that they may be easily duplicated *in vitro,* while others appear to be practically beyond artificial control. What is true of the liver is true of other organs where matter undergoes change. In the blood the presence of several of these ferment agents has been shown.

These various observations have had an important bearing on a discussion which has been of long duration. Since the days of Lavoisier physiologists have been trying to define the means by which the oxygen taken in by the lungs effects the oxidation of the food stuffs. Sugars and starches consumed yield finally water and carbon

dioxide. In this oxidation just as many heat units are liberated as would be set free by the same kind of combustion in a calorimeter. If work is done at the expense of the consumed food stuffs it has been found that the animal makes a somewhat greater return of mechanical energy than is possible with the best machines known. But while all this is interesting and important, it leaves the main question still unanswered: How is it accomplished? To effect such oxidations artificially would require very high initial temperatures. We can not burn sugar by the aid of the oxygen of the air except by reaching first a certain kindling temperature. To burn fats or proteins would be equally difficult. Yet in the animal body, and in the presence of fluids with a mean temperature below 40° Centigrade, the oxygen given up from the arterial blood accomplishes these combustions continuously and with a regularity corresponding with that of respiration. The theories advanced to account for this oxidation have been many and all more or less unsatisfactory. By some it was supposed that the oxygen was first thrown into an active form like ozone, for example. The old Berzelius notion of catalysis was even fifty years ago advanced as a hypothesis, but nothing definite was suggested as to the nature of the catalytic agent. It is an interesting fact that after years of fruitless theorizing chemists are coming back to the idea of catalysis, but from a very different standpoint. The peculiar catalyzing agents active in so many ways in the body are now often assumed to be some of the so-called oxidizing ferments or oxidases. The theory of the oxidases is of rather recent development and there seems to be no question of the existence of these active principles in many vegetable products. Their actual presence in the animal fluids is not so readily demonstrated, but as a result of experiments a great many investigators have been gradually brought to accept this idea as a fact. What Ludwig forty years ago pointed out as likely is actually coming to pass. Chemical physiology is becoming largely a study of catalytic reactions.

Among all the animal oxidations great interest attaches to the combustion of sugar in man. In the digestion of carbohydrates some hexose sugar is finally produced and absorbed and then carried by the portal circulation to the liver. There it is temporarily stored up as glycogen, and, as required, is thrown out into the blood stream again to be oxidized for the needs of the body. Normally this oxidation takes place very quickly and no accumulation of sugar in the blood follows. But under certain conditions the oxidation of the sugar becomes very imperfect or fails entirely, and to maintain the proper osmotic pressure in the blood the excess of sugar escapes by way of the kidneys. This is the situation in the disease known as diabetes mellitus. There are few pathological conditions on which more has been written. We can not say yet that the ultimate cause of diabetes is known, but many facts have been established by chemical investigation and quite recently the work of Cohnheim has shown, apparently beyond question, that for the normal oxidation of sugar the action of two enzymic bodies of distinctly different origin is required. One of these, as might naturally be expected in the light of earlier knowledge, is furnished by the pancreas, while the other comes from the muscles. The oxidation takes place, or may take place, in the fluid surrounding the muscular fibers. Cohnheim has shown that the cell structures as such are not concerned in this oxidation, as it may be brought about in clear filtered solutions from mixtures of finely ground muscle and pancreas. It is, therefore, a chemical process and one of the most interesting thus far studied. Not the least interesting and important fact

connected with the observation is this, that two bodies at least are concerned with the sugar in the reaction. One of these may act as a catalyzer for the other, or, taken together, both may act in the manner of the complement and intermediary body of Ehrlich, of which more will be said below. The point of importance here is that the theory of this oxidation has shifted around so as to become a strictly chemical one. As long as some specific action of the cell was called in to account for the observed phenomena the biologist rather than the chemist was interested in the solution of the problem. It now appears that the chemical factors are the main ones to be considered in the final effect. It remains, of course, true that the oxidizing ferments must be always the products of cell action, but the important idea suggests itself that they need not necessarily be produced by the same body which is later to use them. If investigators succeed in showing more specifically the nature of the two substances, it may be found possible to secure them from other animals and introduce them when needed, much as antitoxins are introduced.

Many of those present doubtless recall the beginnings of what is known as the germ theory of diseases. From his success in developing a satisfactory theory of alcoholic fermentation, which became of vast importance in the brewing and wine industries, Pasteur was led to study the causes of failure often noticed in practical fermentation. Beers and wines sometimes become diseased and spoil in the process of making. They turn sour, or for other reason become unfit for use. The explanation of this was found to lie in the presence of foreign ferments which induce new reactions. As a preventive of such diseases sterilization and pasteurization processes were suggested and have become common in many industries besides those for which first developed. From sick beers and wines Pasteur was led to study sick silkworms, then a question of great commercial interest in France, and found the cause of the malady and later a method of prevention. Following this wonderful work, men began to look for microorganisms elsewhere, and in the course of a few years specific bacteria were described as the active agents in inducing cholera, anthrax, tuberculosis and other dread diseases. According to the germ theory, the invasion of certain tissues of man or the higher animals by these bacteria is the real cause of the disease in question. It must be recalled that these organisms are extremely minute. Many millions of them would be required to produce the volume of a pin head, and that anything so small could give rise to cholera or typhoid fever seemed at first utterly unreasonable. That these minute things are the actual agents of many diseases there can now be no doubt. It remains to discover how they act. At first their effects were assumed to be largely mechanical and in the direction of the destruction of tissues, but in many cases the tissue destruction is of secondary importance. The notion gradually developed that many of the disease-producing bacteria are active through the poisonous principles or toxins which they elaborate. The toxins are complex chemical substances resembling in properties some of the alkaloids, or possibly belonging to the group of enzymes. At any rate, as soluble chemical agents, they are able to diffuse throughout the body and interfere with its normal functions. We appear to have then a chemical theory back of the germ theory and this development is proving of the highest importance from both theoretical and practical standpoints. The theory of the production of toxic substances by the bacteria involved, of course, no new assumption. Chemists had been long fa-

miliar with the production of poisonous matters by other vegetable cells, and the development of ptomaines, or cadaver poisons, was sufficiently well understood to suggest at once the formation of analogous substances in the living organism. Hence the doctrine of the toxins as the important chemical factors in the causation of certain diseases, when once clearly stated, made rapid headway and is now very generally admitted and recognized. The investigation of bacterial intoxications has become a chemical problem of rare fascination and importance, and through this work entirely new departments of research have been opened up, bringing into the practise of medicine, as well as into the literature, new ideas and new methods. The development of the notion of toxins was followed by that of the antitoxins, the potent agents which check or prevent the harmful work of the toxic ferments. The theory of the action of these substances on each other is largely a chemical one and is founded on a basis of experiment. It appears that in many cases studied toxin and antitoxin combine in fairly definite and constant proportions, which would necessarily be the case if their union is in any sense a chemical one. The behavior of one with the other has been compared to that of an acid with a base, but it is more like the combination of active salts to form complex double salts of entirely distinct properties. The extreme toxicity of potassium cyanide, for example, is modified by combination with iron compounds to produce the salt of a new and far less potent acid.

Few topics in medicine to-day attract the attention given to natural and acquired immunity. The history of scientific investigation in this field is not old, but already its literature has become enormous. Immunity may exist with reference to bacteria, or to the toxins produced by bacteria, and in either case it may be inherent or natural or it may be imparted. The natural immunity of many animals to bacterial invasion does not necessarily involve any direct chemical action, and in the most widely accepted notion yet advanced to account for this kind of immunity certain large cells of the body, which have been called phagocytes, or devouring cells, play an important part. These seem to seize upon the foreign invader and destroy it by a kind of digestive process. Such a property is observed in the large white corpuscles or leucocytes of the blood, and it is likely that a chemical action is indirectly concerned here. The cells may produce some specific chemical substance which is a poison for the attacking bacteria. It has also been held that in the gradual and spontaneous disintegration of these cells substances are thrown into the serum which have the real germicidal action. These are the alexins of Buchner, and in the theory of the latter they are enzyme-like substances. What the exact facts are we do not know, but I refer to the point to emphasize the growing tendency to look for the chemical factor in every body phenomenon.

In the study of acquired or developed immunity to bacterial toxins we find the most ambitious introduction of purely chemical theories. In this field the labors of Pfeiffer, Buchner, Bordet, Ehrlich and others are preeminent, and in all cases the chemical idea appears as an essential factor. This is peculiarly true of the so-called 'side chain theory' of Ehrlich, which at the present time attracts the widest attention. Years ago Pasteur introduced the notion of molecular asymmetry into chemical science and pointed out in effect the importance of the conception of configuration in dealing with certain problems. In 1894 during the progress of his famous investigations on the bodies of the sugar group, Emil Fischer published some remarkable

papers on the behavior of certain enzymes in the fermentation of sugars, in which he pointed out that in order to work as ferments the enzymes must possess a certain stereo-chemical structure, bearing a definite relation to the stereo-chemical structure of the sugar. Without this relation fermentation can not take place. In order to make his meaning plain Fischer employed a figure which has since become famous. He said, in speaking of certain glucosides: 'Enzyme and glucoside must fit into each other as a key into a lock in order that the one may be able to exert a chemical action on the other.' In one of these papers Fischer suggests that the idea of related molecular configuration of enzyme and fermentable body may prove of value in physiological investigation as well as in chemistry. We have apparently in this prediction of Fischer made ten years ago the basis of the Ehrlich hypothesis.

Without going into minute details, the Ehrlich notion of bacterial or toxin action on the cells of the body, and immunity from the same, is briefly this. Bacteria, animal cells and toxins are all complex aggregations of more or less complex molecules. The latter have certain configurations dependent on the presence of side chains or side groups, to borrow an expression from organic chemistry. These side chains are directly or indirectly the points of attack or defense in the action of the several bodies on each other. In order that a substance may behave as a poison or toxin to cells of the body, both cells and toxins must, therefore, possess certain reciprocal configurations. It has been suggested by Ehrlich that it is through the presence of these side groups that the cells absorb their necessary nutriment and elaborate new structures from it. Some of the side chains may be constructed to combine with fats, some with carbohydrates and some with proteins, but in the presence of toxins or bacteria with the right kind of side chains combination with these may take place instead. Certain phenomena seem to indicate that this combination is not a direct one, at any rate not always direct, and the conception of an intermediary body or linking complex has been developed. This intermediary body must itself possess two groups with special configurations; one of them fits it to combine with the cell, while the other brings about the combination with the toxic molecule.

The complicated nomenclature called into existence to describe and express satisfactorily the conceptions of this interesting theory appears at first sight a great drawback in the way of readily following it. There are cytophil groups and toxophil groups, and both of these may be called haptophorous groups because they carry the combining or uniting property. Other terms employed sound equally strange to the chemist, but a little patient study discloses what is meant and we are obliged to recognize in the new doctrine an important widening out of biochemical science. Of course no one assumes that the theory, or the various other theories which have grown up around it, will persist in the present form. The chemistry of living things is admittedly the most complex of all kinds of chemistry. For new ideas we must have new figures and these of Ehrlich in the side chain theory are not more unreal than were the figures employed in the early days when a general chemistry began to be evolved from the atomic theory of Dalton. Besides this, the stereo-chemical speculations of Ehrlich and his school present for the first time a tangible working hypothesis to account for the phenomena of toxicity and immunity. In many respects the hypothesis or theory will suffer modification and so discard what is useless or false. But already it has stimulated investigation enormously and created in

medicine a situation analogous to that created in chemistry by Pasteur and van't Hoff and developed largely by the latter and Fischer. In this new medical chemistry there is the same distrust to overcome which was encountered by van't Hoff in the first years after the publication of his work on chemistry in space. It may be recalled that Kolbe especially was very bitter against what he called idle speculation and this is the attitude to-day toward an attempt to explain obscure phenomena in etiology in chemical language. It is true that complete chemical explanations of pathological conditions are in most cases not yet possible, but the bold speculations of Ehrlich, Buchner, Bordet and the other scientists who have contributed to the discussion deserve cordial recognition. It is no fatal objection to their hypotheses that the leaders in the various schools differ as to details. The fact of permanent value is that they are all at work on a theory which is essentially chemical.

The organic chemistry of the protein substances has advanced far enough to show that these bodies are complex aggregations of certain large and small groups. The elimination or destruction of some of these groups may not necessarily mean destruction of the whole molecule. Doubtless it may remain a protein with several of the smaller groups lost. Outside of the animal or vegetable organism there is apparently no simple way of regenerating what has been obliterated. In the living tissues, however, the proteins may possess the power of self-regeneration by some kind of a synthesis; the loss of a few amino groups, for example, need not be followed by the decay of the whole. These amino groups may be convenient points of attack for certain reagents, but not for others. They are, in a sense, the toxophil groups by means of which outside connection is made, but if the proper attacking agent is not used the protein remains unchanged. It is also true that certain reagents may increase the stability of the protein and inhibit practically its destruction under given conditions. In general such molecules possess greater stability in presence of their dissociation or reaction products. Conceptions somewhat analogous to these are included in the Ehrlich immunity theory, according to which some of the separated side chains from the over-stimulated cell behave as antitoxins to check further action.

In still another important direction the influence of chemistry is being felt in medicine and it is the new physical chemistry which is now the vitalizing force. In one of his earlier papers van't Hoff called attention to what this kind of chemistry might do for physiology, and in recent addresses he has come back again to the subject. Ostwald has many times, and even more strongly, pointed out the importance of physical chemistry to the progress of medical theory. As long as physiology alone was concerned in this advance the influence on practical medicine remained somewhat problematical. The clinician has been almost as skeptical about the value of pure physiology as he has been about the value of pure chemistry. But many of the newer developments from the theory of solutions have been found applicable in questions of pathology, the recognition of which fact is of growing importance. A few of these so-called practical applications may be mentioned here.

It is a well known yet always interesting fact that the osmotic pressure of the blood remains within narrow limits a constant. A slight increase following meals or a decrease following large consumption of water is speedily corrected through the activity of the kidneys. The importance of this constancy in osmotic pressure appears when it is recalled that all the other organs of the

body are more or less surrounded by the blood and necessarily in equilibrium with it. Any great variation in the osmotic pressure of the blood would, therefore, be followed by a change in the content or concentration of every dependent cell. It appears to be a special function of the kidney, therefore, to eliminate just enough of the accumulated blood products to keep this mean osmotic pressure at its normal value. If in any given case a wide divergence from this is found by experiment, the conclusion is at once drawn that some serious impairment of the kidney has taken place. The test is easily made with a small amount of the blood by what is known as the cryoscopic method. Its diagnostic value is generally recognized.

Similarly, we have in the determination of electrical conductivity another simple method of finding a certain kind of solution content. This method may be applied to body fluids, especially to the urine and to the blood, and the information secured has often considerable value, since it is not exactly the same as may be obtained by the methods of chemical analysis. The general procedure has been applied in other kinds of work, twenty years or more, but only within the last four or five years have the applications in medicine been thought of. It will be recognized that these applications are comparable to new methods of analysis and their value must be measured from that standpoint.

But the chief value of physical chemistry to medicine does not lie in this direction, practical as it may appear. The development of the modern theory of solutions has wrought a most wonderful change in our mode of thinking of chemical problems, and while for a time this change was noticeable mainly in the treatment of questions of inorganic chemistry, it has finally appeared in the discussion of medical problems also. In pharmacology the conception of independent ions is a helpful one in explaining many points in the action of drugs which have hitherto been obscure. It is well known that the chemical activity of many substances in solution may be greatly modified by the presence of other substances having like ions free. Physiological activity, it is found, is often modified in the same manner, and beyond question the problem here presented will be found a fruitful one in the theory of medication and in the explanation of incompatibles. The importance of certain ions in the blood and in the muscular juices has just begun to be clearly recognized and the maintenance of these in right amount, even when only traces may be present, is a chemical necessity. It is known that the inorganic substances which yield ions have a necessary duty to perform in the body. The constancy of the one per cent. of mineral substances in the blood is doubtless more necessary than the constancy of the twenty per cent., or more, of organic substances.

The physical chemists have given us a number of new general methods of attacking old problems. Some of them have an important bearing on live questions in medicine. For example, take the question of the solubility of uric acid and the urates, the deposition of which in the tissues is supposed to be the source of many disorders. For fifty years or more much has been written on the problem of dissolving these urate deposits or concretions, or of preventing their formation. Lately several writers have begun to study this ever-interesting topic from the standpoint of the mass action law and dissociation hypothesis, and in a way which promises much for the clearing up of the fundamental conditions of deposition. It has already been pretty well shown why certain suggested remedies have not been of value and can not possibly do what was long claimed for them. In the uric acid problem two fundamental ques-

tions are involved; one of these has to do with its formation in metabolism. The other is a question of chemical equilibrium at a given temperature. The first question is the more difficult and also practically the less important. The second question may not prove difficult of solution.

I have spoken of the great work of Ehrlich and others in the development of the doctrines of immunity and toxicity. In the experimental examination of this problem it was found that many reactions between toxins and antitoxins can be carried out in the test-tube, leaving for the animal experiment certain final or crucial reactions only. In other words, a large number of important points in question seem to be strictly chemical and must be tested by chemical rather than by biological methods. In deciding on the nature of any given reaction taking place in solution and requiring time for its completion a determination of the so-called speed of the reaction is often of value. It has been shown that reactions taking place in one direction and involving one, two or three molecules follow certain definite schemes. The behavior of some of the simple ferments has been studied from this point of view and lately it has been found possible to submit the reaction between toxins and antitoxins to this kind of mathematical analysis. Something over a year ago Arrhenius and Madsen published a very important paper with the title: 'Applications of Physical Chemistry to the Study of the Toxins and Antitoxins,' in which, from the observations of Ehrlich, the essentially chemical nature of these reactions was shown. This paper was followed by others by the same authors and also by Ehrlich, who takes exception to some of the physico-chemical generalizations, yet recognizes the value of the mathematical treatment. It is likely that this discussion is but the beginning of the application of physical and mathematical chemistry in the exact study of problems which at one time were assumed to be essentially biological. I believe that medical science will derive great benefit from this alliance, as a means is here offered of testing the value of many assumed working hypotheses. There is a field here which is worthy of attention and which certainly can not remain long unoccupied. Many reactions taking place normally in the body will be found to lend themselves readily to the physico-chemical treatment and the applications in pathology will also appear as the methods become better understood.

Many medical men are beginning to recognize the value of this line of inquiry in the development of research, and the question is often asked how may the practitioner of medicine make himself familiar enough with the new physico-chemical theory to derive any benefit from it. This is admittedly a difficult question. With the student of medicine, however, the case is different. He may be given from the start the proper training to enable him to understand something of the drift of this new chemistry, if not to practise it readily. An opinion has been cultivated for years in some of our medical schools that the only part of chemistry really important for the physician is the organic chemistry of the food stuffs and their metabolic products. This is an extremely narrow conception of the case and it has often led to a neglect of those branches of general and physical chemistry through which the foundation principles of the science may be most satisfactorily presented. With the growing importance of the applications of physical chemistry in medicine the chemical training of the medical man will have to be correspondingly advanced, and of necessity the foundation work in this training will have to be done in the freshman and sophomore years of our scientific

schools and colleges, since few medical schools will have the equipment or be able to afford the time to do it properly. Physiological chemistry will become then a first-year study in all of our medical courses, and the young man beginning the study of medicine must bring with him a knowledge of general inorganic and organic chemistry sufficiently broad to enable him to grasp the new problems which medicine now presents.

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SCIENTIFIC BOOKS.

Handbuch der Fischkrankheiten. Von Dr. Bruno Hofer, Professor der Zoologie an der tierärztlichen Hochschule und Vorstand der Kgl. Bayer. Biol. Versuchsstation für Fischerei in München. Mit 18 Farbentafeln und 222 Text-Abbildungen. Verlag der Allg. Fischerei-Zeitung, München. 1904.

This is the first book devoted exclusively to the diseases of fishes, a volume of 359 pages well printed and well illustrated. The author asserts that the first aim of his work has been to aid the practical fish culturist and secondarily to gather together the substance of the few widely scattered scientific papers on the subject and his own unpublished material, the result of his observations as director of an experiment station. No technical knowledge is necessary to make use of the book. Particular diseases are described under the heads of external symptoms, course, cause, cure and prevention, the pathological changes receiving but passing notice. The scope of the work is limited to middle Europe and to fresh-water fishes alone, with Siebold's 'Die Süsswasserfische von Mitteleuropa' as a basis of nomenclature.

The book is divided into four sections. These treat of general infections, diseases of special organs, the crayfish disease, and general measures against fish diseases. Fourteen bacterial diseases are described, of which six are regarded as specific infections, and the characters of the organism are summarized. The disease itself is given a distinctive name, as 'furunculosis,' 'purpura cyprinorum,' 'pestis salmonis,' etc. The last is the widely known so-called fungous disease of salmon which engaged the interest of Huxley, who believed it to be caused by *Saprolegnia* alone. Dr. Hofer accepts the work of Patterson, who holds the fungus to be a secondary or terminal attack and describes '*Bacillus salmonis pestis*' as the primary cause. It is further interesting to note that the bacillus of tuberculosis is found in fishes, a form recognizably different from the parasite in man and not pathogenic for warm-blooded animals. Seven other organisms are found associated with disease, but their rôle is not regarded by the author as satisfactorily determined. Infections of fishes with bacteria and animal parasites are not unknown in this country, but serious epidemics due to them have been described only among domesticated fishes, while in Europe they seem to be more common and devastate alike the natural habitats as well as the ponds of breeders.

Two general infections with protozoan parasites are described, each caused by a myxosporidian of the genus *Myxobolus*. A systematic list is given, profusely illustrated and with a short characterization of each species, of the sporozoa parasitic for fishes, in which Gurley's U. S. Fish Commission paper is largely drawn upon. This plan of illustrated synopses of the species is carried out with each group of parasites, more extensively with the crustacea.

The second section occupies two thirds of the book and is taken up with local diseases. The skin affections receive most attention and its lesions are mainly caused by parasites, the most important being the saprolegnious fungi, the great enemy of domesticated fishes. None of the tissues or organs is without its pathologic affection. Even the nervous system is the seat of parasitism, the author himself having investigated a yet unnamed sporozoan which causes in trout 'taumelkrankheit,' a torpor finally ending in death. Other authors have described 'polyneuritis parasitica' due to a *Myxobolus*, and a parasitic worm. A short chapter is given to an unexplained exophthalmia, a symptom frequently seen as a